Structure

In This Issue

Molecular Aerobics of DNA Topoisomerase VI

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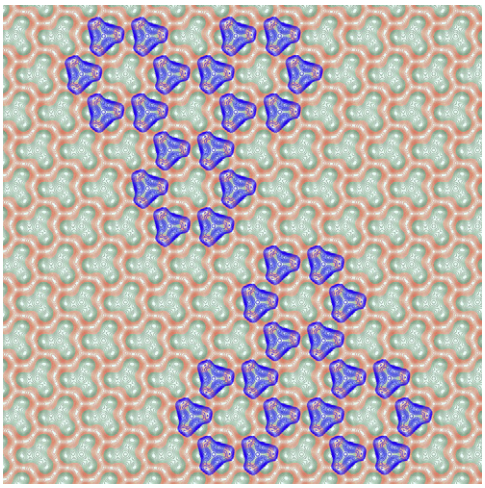
In order for DNA replication to occur, the supercoil of double-helix DNA must first be unwound. DNA topoisomerases are a class of enzymes that removes DNA supercoils by first breaking DNA strand(s) and then resealing the cut. Graille et al. now show that DNA topoisomerase VI adopts a widely open "V" shape, ready to be loaded with DNA, in both apo form and bound to radicicol, a small molecule inhibitor. The authors discuss the extent and nature of molecular rearrangements during the reaction cycle, which leads them to propose a structural model for the two gates DNA transfer mechanism.

Colicin N Skips the Pore and Goes for the Lipid



PAGE 371

Cells are surrounded by membranes across which they transport a variety of molecules, including proteins. Protein translocation is generally believed to occur through membrane protein pores. Recently, the evidence that the membrane's lipid component is a part of the pathway started to accumulate. Baboolal et al. now show that bacterial toxin Colicin N, a 42 kDa protein that kills bacteria by penetrating their outer membrane, translocates via the outside of its receptor protein rather than through a wholly proteinacious pore. This suggests that membrane protein-lipid interface represents an alternative protein translocation pathway. (Figure credits: Baboolal et al.)

Regulation of Enzyme Localization by Polymerization

PAGE 380

Sterile Alpha Motif (SAM) domains are common protein modules found in a many different regulatory proteins. Some SAM domains form polymers that create scaffolds for the construction of large regulatory complexes. Harada et al. discover a different role for SAM domain polymers: they can be used to sequester regulatory proteins in an inactive cellular location.

PerCR Monomers Go to Peroxisome

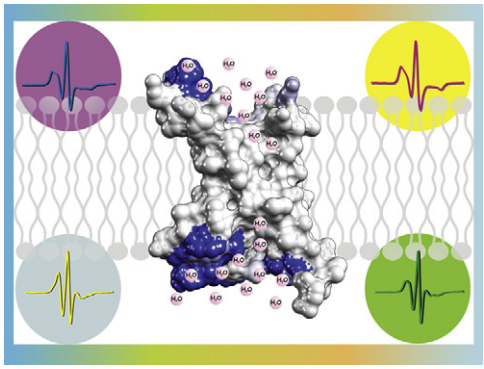
PAGE 388

Pig heart peroxisomal carbonyl reductase (PerCR) belongs to the short-chain dehydrogenase/reductase family, and its sequence comprises a C-terminal SRL tripeptide, which is a variant of the type 1 peroxisomal targeting signal (PTS1), SKL. PerCR structural analysis, done by Tanaka et al., revealed that the C-terminal PTS1 of each subunit of PerCR was buried in the interior of the tetrameric molecule and involved in intersubunit interactions. Thus, cytosolic receptor Pex5p recognizes the monomeric form of PerCR, with exposed C-terminal PTS1, targeting PerCR to peroxisome, where the tetramer is formed.

Isolated-Voltage Sensor Domain in Lipid Bilayer

PAGE 398

Voltage-gated ion channels play a critical role in maintaining the electrical excitability of cells. A strong interplay between the voltage-sensor domain (VSD) and the pore domain (PD) underlies these channel functions. Here, Chakrapani et al. employ EPR spectroscopy to show that the isolated-VSD of KvAP can remain monomeric in reconstituted bilayer and retain a transmembrane conformation. Just as in the full-length channel, the authors find that water-filled crevices extend deep into the membrane. This scaffold is conducive to transport of proton/cations and may underlie the functioning of voltage-sensitive proteins that share a similar molecular architecture of the VSD. (Figure credits: Chakrapani et al.)



Alternative Splicing Behind Bridging Neural Synapses

PAGE 410 and PAGE 422

Presynaptic neurexins (NRXs) bind to postsynaptic neuroligins (NLs) to form Ca^{2+}-dependent protein complexes that bridge neural synapses. NRXs bind NLs through their membrane-proximal LNS domain, which contains a single site of alternative splicing. Prior studies suggest that the β-NRX splice form choice may function to modulate binding between neurexins and neuroligins. Koehnke et al. show that splice-inserted sequences do not partake in direct interaction with neuroligins, which raises the possibility that β-NRX insertion sequence 4 may function in roles independent of neuroligin binding. In related study, Shen et al. unveil that the incorporation of a splice insert into neurexin 1β dramatically reshapes the binding site for neuroligins, revealing the mechanism by which neurexin 1β splice isoforms can acquire neuroligin splice isoform specificity.

OST Groove as a Tunnel for Sugar-free Nascent Polypeptide

PAGE 432

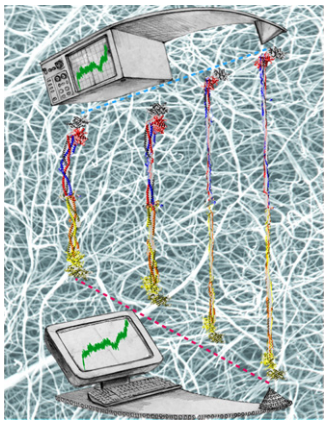
N-linked protein glycosylation is catalyzed by a large transmembrane protein complex, oligosaccharyl transferase (OST), located in endoplasmic reticulum membrane. OST operates synchronously with the translocon, transferring oligosaccharide chains from a lipid carrier to specific sites on nascent polypeptides emerging from the translocon. Li et al. describe a structure of the oligosaccharyl transferase complex at 12 Å resolution, giving support to the hypothesis that the nascent polypeptide is oriented horizontally to the membrane while glycosylated.

"Primed State" in the GroEL Chaperonin Pathway

PAGE 441

GroEL, an ~800 kDa 14-mer, is a nano-cage in which protein folding takes place. Ludtke et al. use electron cryomicroscopy to solve the structure of solution-state GroEL at ~4 Å resolution. De novo modeling tools were developed and used to trace the polypeptide backbone of GroEL directly from the cryo-EM map. The models reveal a previously unseen asymmetric conformation of the two rings, which may represent a "primed state" in the chaperonin pathway.

Molecular Basis of Fibrin Clot Elasticity



PAGE 449

A blood clot must fulfill the paradoxical dual role of being both mechanically stable to stop hemorrhage yet elastic enough to buffer blood's shear forces. Fibrin, the main component of a blood clot, possesses considerable elasticity, but the molecular basis of this elasticity is unknown. Now, Lim et al. probe the elasticity of single fibrinogen molecules and fibrin protofibrils by a combination of atomic force microscopy and steered molecular dynamics simulations. The elasticity of fibrinogen arises from the sequential architecture of its coiled-coil helices. Alterations to the coiled-coils through mutations or disease may interfere with fibrinogen function, changing the elasticity of the fibrin clot and thus causing life-threatening thromboembolism. (Figure credits: Lim et al.)

ErbB4 "Asymmetric Dimer" Activation Mechanism

PAGE 460

The EGF/ErbB family of receptor tyrosine kinases comprises four members that mediate essential cell growth and differentiation events in animal development. Abnormal ErbB function has been implicated in many human cancers, and several ErbB-targeted drugs have proven effective cancer therapies. Qiu et al. report structural and functional characterization of the ErbB4 kinase and show that the "asymmetric dimer" activation mechanism recently described for the EGF receptor (Zhang et al., 2006 [Cell *125*, 1137-1149]) is conserved in ErbB4. A crystal structure of the ErbB4 kinase domain complexed with the pan-ErbB inhibitor lapatinib (Tykerb), recently approved for treatment of breast cancer, is also reported and reveals molecular details of ErbB4 inhibition by this drug.

Closer View of DNA-dependent Protein Kinase Catalytic Subunit

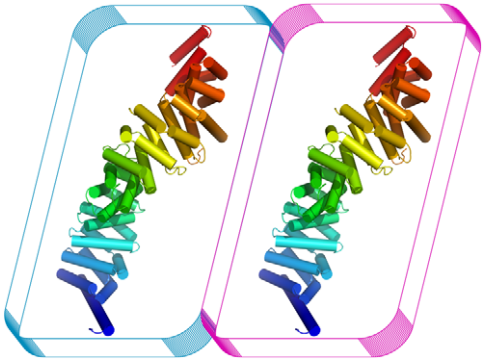
PAGE 468

Mammalian DNA double-strand breaks are repaired primarily by the nonhomologous end-joining pathway. Molecular defects in this repair pathway result in sensitivity to ionizing radiation, a predisposition to cancers, and severe combined immunodeficiency. The DNA-dependent protein kinase catalytic subunit (DNA-PKcs) regulates nonhomologous end joining in mammals. The structure of this large ~0.5 MDa kinase has been characterized by cryo-EM to subnanometer resolution, as reported by Williams et al. α helices and regions of short helical HEAT-like motifs are all resolved in the cryo-EM density. An observed α-helical protrusion in the central channel of the molecule may serve to detect and bind dsDNA ends.

Full-Length β-Catenin's Tale of Two Tails

PAGE 478

β-catenin plays critical roles in both cell adhesion and Wnt signaling by forming protein complexes with different partners. Deregulation of β-catenin is tightly associated with several human diseases, including cancers. Previous structural studies on β-catenin have focused on the armadillo repeat domain. Here, Xing et al. report the first crystal structure of a full-length β-catenin. In addition to armadillo repeats, the C-terminal domain of β-catenin also forms a part of its superhelical structural core, important for protein-protein interactions. The structure rules out tight intramolecular interactions between the β-catenin terminal tails and the armadillo repeats domain.



Megadalton Cell Wall-Associated Adhesion Protein Ebh from *Staphylococcus aureus*

PAGE 488

Staphylococcus aureus genome codes for a huge, 1.1 MDa protein, Ebh. Tanaka et al. investigated the structure of a giant protein of staphylococci, Ebh, homologous to extracellular matrix binding protein, thought to be expressed on the cell surface. The authors report that Ebh is a rod-like molecule 320 nm in length with some plasticity at module junctions. Although not much is known about this giant protein, it has been reported that Ebh can bind to fibronectin and that covering the bacterial surface with Ebh would help with host cell binding. Additionally, Ebh might have a role in maintaining the bacterial cells rigidity. Structural information now available will enable further functional characterization.

